Remarks

Claims 1-78 are pending in the application. Claims 25, 28, 34-36, and 41-44 have been withdrawn from consideration by the Examiner. Examiner is requested to clarify the status of claim 71 since the Office Action says that claim 71 has been rejoined on page 2 and later says that claim 71 remains withdrawn on a second page 2. Claims 1-24, 26, 27, 29-33, 37-40, 45-70, and 72-78 stand rejected. Claims 1, 2, 65, 69, and 73 have been amended, and claims 3-6 and 64 have been canceled. New claim 79 has been added. Support for claim 79 can be found in the Specification on page 35, line 12, through page 37, line 7, and on page 59, line 18, through page 60, line 17. Applicant respectfully requests reexamination and reconsideration of the case in light of the following remarks. Each of the rejections levied in the Office Action is addressed individually below.

I. Rejection under 35 U.S.C. § 102(b) or § 103, in view of Grinstaff *et al.*, U.S. Patent 5,639,473. Claims 1-24, 26, 29, 30-33, 37, 39-40, 45, 46, 47, 49-62, 65-70, and 73-78 stand rejected under 35 U.S.C. § 102(b) or § 103(a) as being anticipated by or obvious over Grinstaff *et al.* (U.S. Patent 5,639,473). The Examiner maintains that Grinstaff *et al.* teach the making of microparticles with a matrix consisting of two components selected from a lipid, a protein, and a sugar. The Examiner also states that the microparticles can be formulated to incorporate a stabilizer such as PEG or a synthetic polymer. This, however, too simply states what Grinstaff *et al.* disclose. Grinstaff *et al.*, in fact, disclose microparticles with a substantially cross-linked polymeric shell made of biocompatible material cross-linked by the presence of disulfide bonds (col. 6, lines 13-14; col. 8, lines 8-10). In column 8, lines 34-53, Grinstaff *et al.* further describe the materials of the polymeric shell as bearing sulfhydryl groups, disulfide groups, or precursors of esters, amides, ethers, and the like that can be used in forming microparticles. Therefore, the materials used in the shell undergo cross-linking during ultrasonic irradiation to create the particles described in Grinstaff *et al.*

In contrast, the microparticles of the claimed invention as amended include three components and do not include a substantially cross-linked polymeric shell. The claims as amended recite microparticles with a lipid-protein-sugar matrix or a matrix with at least three

components selected from lipid, protein, sugar, and synthetic polymer. Although Grinstaff *et al.* list various agents that may be added to their protein particles (see column 12), the only particles that were actually prepared as described in the Examples are protein particles or protein-PEG particles. In particular, nowhere in the Specification is described a particle with a matrix of lipid, protein, and sugar or even a particle with three components in the matrix. At most the particles described by Grinstaff *et al.* have two components—protein and a synthetic polymer. Certainly, a laundry list of materials that might be included in a particle can not suffice to be an enabling and patentability destroying reference with respect to the claimed invention which recites three components in the particles. The inventors of the present application, in contrast to Grinstaff *et al.*, have chosen particular components useful in the preparation of microparticles and have tested their particles and shown that they can be prepared and used successfully for drug delivery. These components used in the inventive particles also do not need to contain sulfhydryl groups for cross-linking. Applicant, therefore, requests that the rejection be withdrawn.

In addition, the microparticles of the claimed invention are prepared without a cross-linking step and therefore would not inlcude a substantially cross-linked polymeric shell as described by Grinstaff *et al.* Support for amended claims 1, 2, 65, 69, and 73 can be implicitly found in the subsection entitled "Methods of Making Microparticles" (beginning on page 25, line 9). This section which describes the preparation of the inventive microparticles does not describe any step which would achieve cross-linking of the matrix components. Specifically, there are no steps using heat, light, or ultrasound to effect cross-linking of the matrix components to form a substantially cross-linked polymeric shell. Therefore, the amended claims find support in the application as filed. In the absence of such a step , the matrix of the microparticles of the claimed invention does not include a cross-linked polymeric shell.

Given the absence of a substantially cross-linked polymeric shell in the microparticles of the claimed invention, Applicant submits that Grinstaff *et al.* cannot anticipate or render obvious the claimed invention. Applicant respectfully requests that the rejection be removed.

II. **Rejection under 35 U.S.C. § 103(a), as being unpatentable over Grinstaff *et al.*, U.S. Patent 5,639,473, in view of Wheeler *et al.*, U.S. Patent 5,976,567.** Claims 1-24, 26, 27, 29-33, 37-40, 45-70, and 72-78 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Grinstaff *et al.* (U.S. Patent 5,639,473) in view of Wheeler *et al.* (U.S. Patent 5,976,567). In addition to the teaching of Grinstaff *et al.*, the Examiner cites Wheeler *et al.* for the proposition that DPPC can be used as the lipid in particles for drug delivery such as those described by Grinstaff *et al.* However, even if Wheeler *et al.* did teach that DPPC can be used as the lipid in particles for drug delivery to enhance the transfection of nucleic acids, there is no motivation or teaching to combine these references, and even if there were motivation to combine these references, Wheeler *et al.* do not overcome the deficiencies in the teachings of Grinstaff *et al.* as described above. And there is no reasonable expectation of success that using DPPC in the particles of Grinstaff *et al.* would lead to the desired characteristics of the particles for drug delivery.

Wheeler *et al.* only teach lipid-nucleic acid particles and nothing more. Wheeler *et al.* do not teach or even suggest the use of proteins, sugars, or synthetic polymers in their particles. Given such a stark disclosure—the particles of Wheeler *et al. only* contain lipid and the nucleic acid being delivered, there would be no motivation to combine these two references. In fact, it would seem to be a teaching away from the addition of other materials such as proteins, sugars, and synthetic polymers to the particles. One of skill in the art would not assume that the addition of a lipid such as DPPC useful in the lipid-nucleic acid particles of Wheeler *et al.* to other types of particles would be useful or effective. Therefore, there is no motivation to combine these two references, and the Examiner has not established a *prima facie* case of obviousness.

Further, even if there were motivation to combine these two references and a reasonable expectation of success, Wheeler *et al.* do not teach that at least three components of the group consisting of lipids, proteins, sugars, and synthetic polymers as recited in the present claims are useful in the preparation of microparticles nor does Wheeler *et al.* teach that components without functionalities for cross-linking are useful in preparing the inventive particles. Without such a teaching to make up for the deficiencies in Grinstaff *et al.*, the references even when combined cannot render the claimed invention unpatentable. Therefore, Applicant submits that even a

combination of Wheeler *et al.* and Grinstaff *et al.* would fail to render obvious the claimed invention given the differences between the combined teachings and the claimed invention. Applicant requests that the rejection be removed.

III. Rejection under 35 U.S.C. § 102(b), as being anticipated by Hanes *et al.*, U.S. Patent 5,855,913, or in the alternative, under 35 U.S.C. § 103(a) as being unpatentable over Hanes *et al.* The Examiner has rejected claims 1-24, 26, 27, 29-31, 33, 37-40, 45-69, and 73-78 under 35 U.S.C. § 102(b) as being anticipated by Hanes *et al.* (U.S. Patent 5,855,913), or in the alternative, under 35 U.S.C. § 103(a) as being unpatentable over Hanes *et al.* The Examiner maintains that Hanes *et al.* teach "a polymeric microparticle of less than 10 μm in diameter for use as a controlled release-encapsulated carrier of biologically active molecules such as DNA or DNA coding for a gene of interest, wherein the microparticles are composed of a combination of biocompatible materials selected from DPPC, copolymers, protein excipients (any known polymeric polypeptide or copolymers thereof) and a sugar (lactose)." Applicant disagrees.

Hanes *et al.* rather teach particles incorporating a surfactant for drug delivery to the pulmonary system. Because of their use in drug delivery to the pulmonary system, these particles are aerodynamically light, having a tap density of less than 0.4 g/cm^3. Hanes *et al.* state that the surfactant may be incorporated throughout the particle or may be coated on the particle's surface. The reference also lists many exemplary surfactants for use in the particles. The surfactant improves various surface properties of the particles including reducing particle-particle interactions. Hanes *et al.* describe the polymeric particles as being formed from biocompatiable polymers such as polyanhydrides, polycarbonates, polyalkenes, and other synthetic polymers; celluloses; polysaccharides; peptides; and proteins. Particles formed from only surfactant and the agent to be delivered are also described. Hanes *et al.* nowhere teach or suggest the particular combinations of materials recited in the claims for use in the claimed invention. The contribution of Hanes *et al.* to the art is essentially the use of surfactants in particles for drug delivery to the pulmonary system and not the use of a combination of components (*e.g.*, lipid, protein, and sugar) to form the matrix of microparticles.

Although Hanes *et al.* may mention each of the materials recited in the claims, Hanes *et al.* do not teach the use of the combination of these materials in the matrix of a particle. The claimed invention recites the use of a combination of three components selected from proteins, lipids, sugars, and synthetic polymers in the inventive microparticles. Hanes *et al.* do not teach that any triple combination of biocompatible materials can be used to make the matrix of the particles as the Examiner has suggested. Hanes *et al.* do not prepare any microparticles with combinations of materials as claimed in the present invention. For example, the examples in Hanes *et al.* describe particles made with poly[(p-carboxyphenoxy)-hexane anhydride], particles made with poly(D,L-lactic-co-glycolic acid) (PLGA 50:50), and particles made with the protein lysozyme, particles made with dextran-DEAE, particles made with trehalose, and particles made with polyethylene glycol. Hanes *et al.* do mention that these particles may be formed with a surfactant such as DPPC; however, Hanes *et al.* do not describe the use of three components in the matrix of the particles as claimed in the present invention. The Examiner mistakenly refers to Example 3 of Hanes *et al.* as describing a combination of lipid, sugar, and polymer. The particles described in Example 3 have FITC-Dextran "dispersed throughout the polymer matrix" of PLGA (the synthetic polymer) and DPPC (the lipid). The sugar, FITC-Dextran, is the "model drug" in the microspheres and therefore does not constitute part of the matrix as in the claimed invention ("matrix comprising lipid, protein, and sugar" in claim 1, or "wherein the matrix comprises at least three components selected from the group consisting of lipid, protein, sugar, and synthetic polymer" in claim 2). Hanes *et al.* themselves do not even consider the FITC-Dextran to be part of the matrix because they say that "the drug [FITC-Dextran] is evenly dispersed throughout the polymer matrix," indicating that the drug to be delivered and the matrix are two separate things.

Hanes *et al.* only describe the use of at most two components—a lipid; and a synthetic polymer, protein, or sugar. Since Hanes *et al.* do not teach or even suggest a combination of three components, Hanes *et al.* cannot anticipate or render obvious the claimed invention. Applicant requests that the rejection be removed.

IV. **Rejection under 35 U.S.C. § 103(a), as being unpatentable over Hanes *et al.*, U.S. Patent 5,855,913, taken with any of Grinstaff, Sutton, Rypacek, and further in view of Wheeler.** Claims 1-24, 26, 27, 29-33, 37-40, 45-69, and 73-78 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanes *et al.* with any of Grinstaff *et al.*, Sutton *et al.*, or Rypacek *et al.*, and further in view of Wheeler *et al.* The Examiner states that Hanes *et al.* do not claim explicitly minor modification such as known DNAs, RNAs, or plasmids encoding for an antigen, ratios of agents being used in the formulations, and/or a particular combination of known matrix polymers (albumin and/or other known polymer), lipids and excipient(s) such as any other sugar (cellulose). The Examiner continues that such modifications would have been obvious to one of ordinary skill in the art as minor modifications that can be practiced as a matter of design choice by a person of ordinary kill in the art of polymers, particularly in view of the totality of the prior art of record as set forth in Grinstaff *et al.*, Sutton *et al.*, or Rypacek *et al.* Applicant disagrees.

As pointed out above, Hanes *et al.* fails to teach a combination of three components selected from proteins, sugars, lipids, and synthetic polymers. The other references cited also fail to teach such a combination of three components in the matrix of the microparticles. Therefore, even when all five references are combined, the combination fails to teach or suggest such a combination.

In addition, even if the combined references taught such a combination of components, there still would be no expectation of success since before the present application it was unclear whether particles made of these components would form stable useful particles. The inventors on the present application conceived of microparticles having a matrix comprised of three components and went on to show that such particles could be prepared, were stable, and were useful in delivering nucleic acids. The combined references did not. The combined references at best merely provide a laundry list of materials that might be tried in the preparation of microparticles. The teachings of the combined references in no way lead to the claimed invention. Therefore, the combined references cannot render unpatentable the claimed invention, and the Applicant requests that the rejection be removed. If the rejection is not removed, the Applicant requests that the Examiner be more specific in the next communication with respect to

which reference is teaching which aspect of the claimed invention so that the Applicant is better able to address the rejection.

In view of the forgoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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